REMARKS

Claims 19-48 are pending in this application. The pending claims are rejected under 35 U.S.C. § 103. For reasons set forth below, Applicants request that the rejections be withdrawn and the pending claims allowed to issue.

1. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Adjei and Waldrep et al., in view of Gilbert, Knight et al. and Applicant's admission on the record. According to the Examiner Adjei, Waldrep, Gilbert, Knight and Applicant admit on the record that the claimed compounds are old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. According to the Examiner, these medicaments are thought as useful for treating graft rejection, inflammation and those conditions claimed and disclosed by Applicant.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the difference between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere,* 383 U.S.1, (1996). The Court of Appeals for the Federal Circuit (CAFC) summarized the legal standard with regard to the showing necessary to support a proper rejection under Section 103 in *In re Rijckaert*, 28 USPQ2d 1955, (1993) as follows:

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness....A *prima facie* case of obviousness is established

when the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. If the Examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned. Id. (citations omitted).

The prior art relied upon by an examiner to establish a *prima facie* case must not only suggest that the claimed device or composition be made or that a claimed method be performed, but the prior art must also provide one of ordinary skill in the art with a reasonable expectation that the claimed subject matter can be successfully used to effect a practical purpose . *In re Vaeck* 20 USPQ2d 1438, 1442 (Fed. Cir. 1991): Thus, the relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In *re: O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Circ. 1988).

In the present instance, the relevant inquiry is whether any of the cited references suggest compositions of non-encapsulated aerosolized cyclosporine and their use for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders.

A review of the Waldrep, Gilbert and Knight references reveals that each of the cited references fails to discloses, or even suggest, a method for prevention of graft rejection in transplant recipients comprising administration of unencapsulated cyclosporine ***directly following transplantation***. Applicant has amended the claims directed to such methods to indicate that following transplantation, the initial dose of cyclosporine is administed to the transplant recipient either "within 10 days following transplantation or prior to the development of symptoms associated with transplant rejection". Support for the amended claims can be found on page 9, lines 12-15, of the specification.

Additionally, Applicant asserts that none of the references suggest the use of compositions of ***non-encapsulated cyclosporine***, much less their use for prevention of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders. In addition, although Adjei discloses compositions of non-encapsulated cyclosporine, Adjei fails to disclose or suggest that such non-encapsulated compositions could be successfully used to prevent graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders using such compositions.

Applicant asserts that the mere disclosure of liposomal formulations of cyclosporine would not only fail to suggest the claimed methods and compositions of the invention, *i.e.*, non-encapsulated formulations of cyclosporine, but also fail to provide any expectation that the claimed methods utilizing such compositions could successfully be practiced.

Applicant's respectfully direct the Examiner's attention to the Rule 132 Declaration of Dr. Aldo Iacono ("Iacono Declaration"), submitted herewith, which sets forth in detail each of the points discussed below. First, one of ordinary skill in the art would recognize that liposomal formulations containing cyclosporine would have altered pharmacokinetic properties, such as biodistribution, clearance rates, and toxicity as compared to non-encapsulated formulations of cyclosporine since a lipid membrane surrounds the active drug product resulting in hydrophobic and hydrophilic aerosol droplet interactions. (¶3, Iacono Declaration)

In addition, a number of references actually teach away from the use of non-encapsulated formulations of cyclosporine....a further indicia of non-obviousness. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F. 2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986).

For example, Knight states in column 2, lines 5-7 that "in laboratory animals the use of liposomes actually reduced toxic effects observed with the drug alone."(¶4, Iacono Declaration) Furthermore, as set forth in Gilbert (1996, J. of Aerosol Medicine 9:111-122), "incorporation of potentially useful drugs into liposomes instead of using free drug has several advantages: solubility of lipophilic drugs allows for much greater concentrations of drug to be used; in many cases, incorporation decreases a drug's toxicity without affecting its inhibitory effects, and liposomal formulations may lead to better pharmacokinetics such that shorter and/or fewer treatments are necessary." (¶4, Iacono Declaration)

However, despite this teaching away, Applicant has demonstrated, unexpectedly, that doses of non-encapsulated cyclosporine as high as 300 mg per day are tolerated by the treated patient as demonstrated by the working examples presented in the specification (Example 6, p.22-28 of the specification).

Furthermore, Applicant maintains that there are a number of potential drawbacks associated with the use of liposomal encapsulated formulations of cyclosporine that can be avoided by the use of the non-encapsulated cyclosporine compositions of the invention. (¶5, Iacono Declaration). For example, Harrington et al., (2002, Journal of Pharmacy and Pharmacology 54:1573) states the following:

> "Formidable difficulties were presented by the need to produce stable drug-containing liposomes in a reliable, reproducible way. The entrapment conditions for any particular agent need to be optimized individually. Because liposomes can carry drugs in three compartments (water-soluble agents in the central aqueous core, lipid-soluble agents in the membrane, peptides and small proteins at the lipid-aqueous interface), a diverse range of optimal encapsulation conditions

> may exist for different agents. In addition, the release kinetics of the entrapped agents can vary, depending on the liposomal formulation, and this can effect the therapeutic efficacy. Therefore, development of agents for preclinical and clinical uses can be both laborious and expensive."

Moreover, the results presented in Bridges et al, (2000, International Journal of Pharmaceutics 204:69-79) demonstrate that selection of both nebulizer and liposome components of the nebulizer-liposome system are critical for drug delivery to the respiratory lung regions. (¶6, Iacono Declaration). Addtionally, as set forth in Desai et al. (2003, Pharmaceutical Research 20:442), it was established that the encapsulation of polymyxin B sulfate, typically a systemic antibiotic, into liposomes reduced its antimicrobial activity indicating that encapsulation of a therapeutic agent into lipsomes can effect the efficacy of the agent.(¶6, Iacono Declaration).

Finally, experiments were conducted that demonstrate the effectiveness of non-encapsulated aerosolized cyclosporine as prophylaxis for lung transplant rejection. (¶7, Iacono Declaration). To measure the dose-response relationship, 15 subjects underwent a one time radionuclide study to measure the lung deposition of cyclosporine. Deposition in the transplant was correlated with physiologic indices of effectiveness as measured by the change in one-second forced expiratory volume (FEV1) over time. Deposited dose in the periphery of the transplanted lung(s) was compared to percentage change in FEV1 at post-operative days 200, 400 and 600. As indicated in Exhibit G of the Iacono Declaration, there was a significant correlation between improvement in FEV1 and dose at all time points.

In addition, Exhibit H the Iacono Declaration shows the average percentage increase in pulmonary function for the group of single lung recipients who deposited $\geq$ 5 mg in the periphery of their transplanted lung(s) (the high dose group). (¶8, Iacono Declaration). Data is also presented

for single lung recipients in the < 5 mg low dose group, and single lung recipients in the placebo. As demonstrated, subjects depositing 5 mg or more experienced an improvement in lung function, whereas placebo subjects, and subjects depositing less than 5 mg tended to demonstrate a decline.

Bronchial obliterans (OB) is the principle obstacle to long term survival after lung transplantation. Experiments were conducted to determine whether aerosolized cyclosporine could confer a survival advantage in lung transplant recipients with OB. 39 lung transplant recipients with histologic OB received rescue therapy with aerosolized cyclosporine for refractory rejection. Survival was compared to two contemporaneous control groups with OB: 51 transplant recipients from the University of Pittsburgh and a multicenter group of 100 recipients from the US, Europe and Australia. The median survival after OB was 4.5 yrs with aerosolized cyclosporine versus 2.4 and 2.3 yrs in the Pittsburgh and multicenter controls. The data indicates that aerosol cyclosporine provides a survival advantage in lung transplant recipients with bronchiolitis obilerterans. (¶9, Iacono Declaration)

Finally, as set forth in Exhibit I of the Iacono Declaration, an increase in the survival rate of patients treated with aerosolized cyclosporine was observed as compared with placebo treated patients further demonstrating the successful use of non-encapsulated aerosolized cyclosporine for treatment of transplant recipients.(¶10, Iacono Declaration)

Thus, despite the teaching away of the use of non-encapsulated cyclosporine as indicated above, the data presented herein demonstrates the successful use of non-encapsulated aerosolized cyclosporine as a prophylaxis for lung transplant rejection. (¶11, Iacono Declaration)

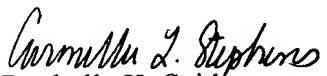
In summary, Adjei and Waldrep, in combination with Gilbert and Knight, fail to suggest the compositions of the claimed invention, *i.e.*, non-encapsulated cyclosporine, nor do they provide a reasonable expectation of success in the use of such compositions for prevention

of graft rejection, pulmonary inflammation and/or inhibition of the immune response associated with T-cell mediated immune disorders. Furthermore, the non-encapsulated cyclosporine of the invention provides compositons and methods for treating pulmonary disorders without the need for optimization of encapsulation conditions. Thus, Applicant respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicant believes that the invention described and defined by the claims is patentable. Withdrawal of all rejections and consideration of the new claims is requested. An early allowance is earnestly sought.

Respectfully submitted,



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